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OSTENSIN - A NEW ANTIHYPERTENSIVE

Trimethidinium methosulfate (Ostensin - Wyeth) is a new ganglion-blocking drug for the treatment of hypertension. It is chemically similar to the quaternary ammonium ganglion-blockers, pentolinium (Ansolysen - Wyeth) and chlorisondamine (Ecolid - Ciba). Some investigators believe that Ostensin may lower blood pressure not only by its ganglion-blocking effect, but also by its action on the central nervous system (R. A. Dunsmore, et al., Am. J. Med. Sci., 236: 483, 1958). The manufacturer does not regard the evidence as conclusive, however, and the hypotensive action of the drug is attributed primarily, if not entirely, to ganglion block. It is unfortunate, therefore, that a drug of this class - generally resorted to only in severe or malignant hypertension - is now being promoted for use even in mild hypertension (one Ostensin advertisement says directly that Ostensin is indicated for diastolic blood pressures over 90 mm., and other advertisements clearly suggest such use).

The greatest hazard with effective doses of ganglion-blocking drugs is postural hypotension, with the risk of syncope and of myocardial, renal or cerebral infarction. Their most common side effects are due to blockade of the parasympathetic system with consequent constipation (in some cases, paralytic ileus), blurred vision, dry mouth and impotence. Attempts have been made to minimize the side effects of ganglion blockers by using lower doses in combination with chlorothiazide and with such centrally acting drugs as reserpine and hydralazine. Such combinations can be helpful, but they do not reduce the hazards sufficiently to extend the usefulness of ganglion-blockers to mild hypertension. The risk of using Ostensin for uncomplicated mild or even moderate hypertension is probably not warranted by any possible benefits to be gained.

CLINICAL EFFECTS - In studies on 19 hypertensive men (W. M. Kirkendall, et al., presented at a meeting of the American Heart Association, Oct. 24, 1958), it was found that the hemodynamic effects of Ostensin were similar to those of other ganglion-blocking drugs. Therapeutic trials (R. A. Dunsmore, et al., see above; and P. Blaquier, et al., Univ. Mich. Med. Bull., 24:409, 1958) suggest that the drug is effective as an antihypertensive agent and that its side effects may be less marked than those of other ganglion-blocking drugs. Since new drugs often appear to be relatively free of side effects which later become more evident, further experience is needed to establish whether Ostensin offers a significant advantage in freedom from unwanted effects.

Although some investigators did not observe the development of tolerance to Ostensin (P. Blaquier, et al., see above; F. H. Smirk, Am. Heart J., 58: 701, 1959), others have reported temporary tolerance in some patients (R. A. Dunsmore, et al., see above). The latter group advises the continuation of dosage during the period of tolerance; they report that no secondary tolerance develops after the initial tolerance is overcome.

ADMINISTRATION - A single oral dose of Ostensin is effective for 8 to 12 hours. Initially, 20 mg. of the drug is taken on an empty stomach before breakfast and before the evening meal; the dose is increased by 20 mg. every third day until the desired lowering of blood pressure (in upright position) is obtained, usually at 120 to 140 mg. total per day. Some patients require a third dose in mid-afternoon to achieve even control (N. O. Bohrani, Ann. Int. Med., 51: 983, 1959). If side effects are troublesome, then a thiazide drug (such as chlorothiazide) or reserpine may be used concurrently, and the dosage reduced. Forty milligram tablets of Ostensin, purchased in quantities of one hundred, cost the patient about 10¢ apiece.

In summary, while Ostensin does not offer a new approach to the therapy of hypertension, it is a useful alternative to the many ganglion-blocking antihypertensives in current use. There is no evidence that it offers a superior kind of blood pressure control, and only longer use will show whether side effects actually tend to be less frequent or less severe. Because of the risk of dangerous hypotension, ganglion-blocking drugs should never be used unless the patient can be effectively supervised and dosage carefully controlled. It is perhaps relevant to comment that the success of antihypertensive therapy may in most cases depend more on the thoroughness of the physician and the endurance of the patient than on the choice of a particular drug (F. H. Smirk, Postgrad. Med., 25: 11, 1959).

SYNTETRIN - A NEW PARENTERAL TETRACYCLINE

Previous Medical Letter reviews of tetracycline preparations have suggested that they be used sparingly because of the growing problem of resistant organisms. The need for caution applies equally to the new intramuscular preparation, N-pyrrolidinomethyl tetracycline, a synthetic modification of the tetracycline molecule (Syntetrin - Bristol).

This and other parenteral tetracyclines should be reserved for patients with severe infections caused by organisms sensitive to tetracyclines, and they should be used in place of oral tetracyclines only with patients unable to take anything by mouth; who have impaired intestinal absorption; or who require frequent intake of food, milk, or calcium or other mineral salts, all of which significantly inhibit the absorption of oral tetracycline.

ANESTHETIC AGENTS - Because intramuscular tetracycline injections are likely to be painful, Syntetrin contains a local anesthetic, Xylocaine. Xylocaine is also present in Terramycin IM (replacing the procaine previously used in this Pfizer preparation of oxytetracycline), and in Bristol's Tetrex IM (tetracycline phosphate complex). Xylocaine is regarded as an anesthetic less likely to

cause allergic reactions than procaine, though procaine itself rarely causes allergic reactions. Since neither agent eliminates painful local reactions, the manufacturers recommend that oral tetracycline replace parenteral as soon as the patient's condition permits.

All tetracycline products, old and new, oral, intramuscular and intravenous, are identical in antibacterial spectrum, in failure to inhibit resistant bacteria, and in ability to induce superinfections by such bacteria in the gastrointestinal tract and other organs. Parenteral administration of tetracycline does not avoid the risk of severe staphylococcus enteritis.

SOLUBILITY OF SYNTETRIN - Bristol claims that Syntetrin is "2500 times more soluble than tetracycline" and that there is an "enhancement of total antibiotic activity ... related to the unique solubility of Syntetrin and its more efficient absorption from intramuscular sites." Irregularity in absorption from intramuscular sites has indeed been a problem with tetracycline IM preparations, and if the unpublished data cited by Bristol are confirmed, then Syntetrin may prove to be more reliable than other IM tetracyclines in producing a prompt and effective blood level of antibiotic. Solubility and rate of absorption of a tetracycline from an IM site are not, however, as important as stability in body fluids, resistance to degradation, and rate of renal clearance in determining persistence of blood levels. The antibiotics experts consulted by The Medical Letter were in full agreement that not enough clinical work has yet been done with Syntetrin to warrant its routine substitution for other intramuscular tetracyclines in the infrequent instances in which such preparations are needed. Furthermore, they do not agree with the recommendation that tetracycline therapy should be initiated routinely with Syntetrin or with any other intramuscular preparation.

In summary, in most infections where a tetracycline is needed, an oral tetracycline should be used. It is capable of producing effective and sustained blood levels in usual doses, especially when taken on an empty stomach -- twice daily for moderate infections and four times daily for more severe infections. For the hospital patient with a fulminating infection demanding the attainment of blood and tissue concentrations in a few minutes, an intravenous (not an intramuscular) tetracycline should be used, and it should be administered over a period of not less than 30 minutes, preferably one hour (but note that in persons with impaired renal or hepatic function, intravenous tetracycline may produce blood levels so high that the antibiotic will act as a toxic agent and interfere with tissue respiration in the brain). IM tetracyclines should, in general, be reserved for patients with severe infections requiring tetracycline, treated outside of the hospital, and who are unable to take the drug by mouth, or who have impaired gastrointestinal absorption.

ANTIBIOTIC PROPHYLAXIS FOR SEVERE TRAUMATIC WOUNDS

Wounds were not listed among the relatively few indications for antimicrobial chemoprophylaxis in a recent Medical Letter review of this subject (1: 81, Oct. 30, 1959). However, clinical and experimental work suggests that antibi-

otics do have a place in the prevention of infection from severe traumatic wounds. The prophylactic administration of suitable antibiotics is, in general, indicated in patients with lacerations or avulsions requiring the use of suture material below the skin surface; and in those with penetrating wounds of the body cavities or viscera; or with compound fractures. In such instances the prophylactic administration of antibiotics restrains local infection and systemic invasion for many hours, thus affording the physician extra time in which to make proper preparations for surgical care of the patient. W. A. Altemeier (Postgrad. Med. 20: 319, 1956) emphasizes the interdependence of prophylactic chemotherapy and surgical care in the treatment of severe wounds.

SPECIFIC MEASURES - In an excellent discussion of the prophylaxis of wounds, D. V. Habif ("Infections and Antibacterial Agents in Trauma," Chap. 3 of Trauma, W. B. Saunders, 1959) urges that swab cultures be taken from all open traumatic wounds. In addition, he says, "... cultures of debrided tissue are valuable in defining the existent bacterial flora and determining its sensitivity to various antibiotics. ... More important than the use of antibacterial agents in the wound at the time of injury is early debridement and irrigation by saline (0.9 per cent) solution, which will remove the major portion of contaminating bacteria. Attempts have been made to further decrease the remaining bacterial population by irrigation, subsequent to debridement, with a combination of ... bactericidal antibiotics in solution, such as bacitracin (1:500), neomycin (0.5 per cent), and polymyxin (0.1 per cent). There is no clear-cut evidence, however, that the added irrigation of the wound with antibiotic solution affords increased protection against local suppuration." With all wounds, foreign material and shreds of skin and subcutaneous tissue of questionable viability should be removed by thorough debridement; pathogenic clostridia organisms cannot propagate in normal tissue.

CHOICE OF ANTIBIOTIC - Antibiotics should be administered for at least five days. If there is no allergic sensitivity to penicillin (see Medical Letter, 1: 87, Nov. 13, 1959 for precautions in administration of penicillin), this is generally considered to be the antibiotic of choice. Habif recommends that procaine penicillin, 600,000 units, be combined with streptomycin, 0.5 gram, both given intramuscularly every 12 hours. Alternative antibiotics are tetracycline and chloramphenicol (Chloromycetin - Parke, Davis). After the initial dosages, however, the choice of antibiotics for continued therapy of open wounds should be determined by bacterial cultures.

Because of the frequency of allergic reactions to tetanus antitoxin, it should be reserved for patients who have not had a full course of toxoid injections within five years. The Presbyterian Hospital in New York follows this procedure: If the interval since active immunization is less than five years, 0.5 cc. of tetanus toxoid fluid is given intramuscularly. If the interval is five years or more, or if the history is uncertain, 1500 to 5000 units of tetanus antitoxin are given intramuscularly after appropriate testing for sensitivity to horse serum. If the treatment of a traumatic wound in a non-immunized patient is delayed, Dr. Habif suggests that the dose of antitoxin should be 10,000 to 20,000 units. This amount provides passive immunity for five to ten days, and it is repeated as indicated, with sensitivity to horse serum being tested before each injection.

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